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NOTARO & MICHALOS P.C.
100 DUTCH HILL ROAD
SUITE 110
ORANGEBURG, NY 10962-2100

EXAMINER	
ORWIG, KEVIN S	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,614	SUBR ET AL.	
	Examiner	Art Unit	
	Kevin S. Orwig	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Dec. 22, 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/22/08, 12/22/08, 12/22/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendments and arguments filed Dec. 22, 2008 are acknowledged and have been fully considered. Claims 9-16 are cancelled; claims 1-8 are amended.

The objection to the specification (i.e. the abstract) is maintained, as discussed below.

The objections to claims are 1, 3-5, and 7 are withdrawn in light of the claim amendments.

The rejection of claim 6 under 35 U.S.C. 112, 2nd paragraph is maintained as discussed below.

The rejection of claim 7 under 35 U.S.C. 112, 2nd paragraph is withdrawn upon further consideration.

The rejection of claim 8 under 35 U.S.C. 112, 2nd paragraph is withdrawn in light of the claim amendments.

The rejection of claims 1 and 3 under 35 U.S.C. 102(b) over GREENWALD (WO 99/30727; Published Jun. 24, 1999) is maintained as discussed below.

The rejection of claims 1 and 3 under 35 U.S.C. 103(a) over Greenwald as evidenced by ULBRICH (K. Ulbrich *et al.*, J. Controlled Release (2000) 64, p. 63-79) is maintained as discussed below.

The rejection of claims 1-8 under 35 U.S.C. 103(a) is maintained as discussed below.

No new grounds of rejection are set forth herein.

Information Disclosure Statement

References lined-through on the information disclosure statement(s) were not considered because they were not provided and/or also lack a date and as such are not fully in compliance with 37 CFR 1.98. Applicants are advised that the IDS forms submitted Dec 22, 2008 are duplicative. Applicants' cooperation is requested in avoiding duplicate citations in order to avoid delays at the time of issue.

Claim Objections

Claim 1 is objected to because of the following informalities: the word "they" in line 4 of the claim should be replaced by the phrase "said reactive polymers and copolymers" or similar claim language.

Claim 1 is objected to because of the following informalities: the word "of" should be inserted between the words "units" and "N-(2-hydroxypropyl)-methacrylamide".

Abstract (Maintained)

The abstract of the disclosure is objected to because the language of the abstract is atypical for U.S. national stage applications. Applicants' amendments to the abstract are noted. However, the phrase "the solution" remains in the abstract (see line 3 of the revised abstract). This language is more proper in international stage applications, and should be changed to "the invention" or the like in order to conform to

common U.S. terminology standards and improve clarity and readability. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112 (2nd Paragraph) (Maintained)

Claims 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants' amendments to claim 6 are noted. However, the phrase "oligopeptides of doxorubicin" remains in the claim (lines 4-5). As stated previously, this phrase is unclear since "peptides of doxorubicin" do not exist and it is unclear what is meant by this phrase. This term is not defined by the claims, the specification does not provide a sufficient standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The examiner suggests eliminating this phrase.

Claim Rejections - 35 USC § 102/103 (Maintained)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by GREENWALD (WO 99/30727; Published Jun. 24, 1999) (hereinafter Greenwald) or, in the alternative, under 35 U.S.C. 103(a) as obvious over Greenwald as evidenced by ULBRICH (K. Ulbrich *et al.*, J. Controlled Release (2000) 64, p. 63-79) (hereinafter Ulbrich).

1. Greenwald discloses prodrugs based on polymeric transport cores (abstract). Greenwald teaches the use of a variety of polymers as the basis of their invention including, *inter alia*, hydroxypropylmethacrylamide (HPMA) and copolymers thereof (page 17, lines 6-10). This teaching makes a distinction between a polymer of HPMA alone and copolymers of HPMA with other polymers. Thus, the HPMA as taught by Greenwald is a homopolymer in at least one embodiment, in which case approximately 100% (i.e. minimally 60%) of the monomer units are hydroxypropylmethacrylamide units. It is noted that conventional usage of the terms hydroxypropylmethacrylamide (HPMA) and polyhydroxypropylmethacrylamide (PHPMA) refer to the 2-hydroxypropyl form of the HPMA monomer (i.e. N-(2-hydroxypropyl)methacrylamide), as evidenced by Ulbrich (page 64, left column, second paragraph; page 65, left column under heading 2.5 Synthesis of Monomers). Furthermore, Greenwald teaches the use of thiazolidine-2-thione groups bound through the nitrogen of the thiazolidine-2-thione group to a carbonyl group that is a component of a linker at the end of the polymer chain (page 5, lines 6-8; examples 1, 5, 8, and 10; figures 2, 3, and 5), reading on claims 1 and 3.

2. Alternatively, given the meaning of HPMA commonly used in the art (see Ulbrich evidentiary reference) it would have been obvious to one of ordinary skill in the art at the time of the invention to use a homopolymer of N-(2-hydroxypropyl)methacrylamide (i.e. approximately 100% of N-(2-hydroxypropyl)methacrylamide groups) as the polymeric core in light of the disclosure of Greenwald.

Response to Arguments

Applicants' arguments have been fully considered but are not persuasive. Applicants argue that Greenwald is directed to a different structure and synthesis than the instant invention (page 8 of the response). Applicants argue that specific reactions are required for the preparation of the instant polymers and that these reactions are not disclosed in Greenwald (page 8 of the response). Similarly, applicants argue that the "detailed structure and length of polymer chain" of claims 1-3 are not disclosed by Greenwald (page 9 of the response).

First, no limitations regarding synthetic parameters, detailed structure, or length of polymer chain are present in the instant claims. In contrast, the instant claims are drawn to reactive polymers and copolymers comprising minimally 60% N-(2-hydroxypropyl)methacrylamide monomer units (these could be linked in any way) and thiazolidine-2-thione at a variety of positions in the polymer. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the process by which the drugs are released from Greenwald's polymers, and the structure and length of the polymer chain) are not recited in the rejected claim(s). Although the claims are interpreted in

light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Furthermore, even if limitations of the synthetic steps used to make these polymers were present in the claims, the claims are drawn to the polymers themselves, and would not be limited to the manipulations of the recited steps, only the structure implied by the steps. See MPEP § 2113.

Second, Greenwald discloses structures that read on the instant claims, contrary to applicants' assertion that Greenwald is directed to different structures. While it is acknowledged that Greenwald is drawn predominantly to the use of polyalkylene oxides (PAO) compounds (e.g. PEG), Greenwald clearly teaches that HPMA can be used as a suitable alternative (page 17, 2nd paragraph). Specifically, Greenwald states: "As an alternative to PAO-based polymers, effectively non-antigenic materials such as dextran, polyvinyl alcohols, carbohydrate-based polymers, hydroxypropylmethacrylamide (HPMA), and copolymers thereof, etc. and the like can be used if the same type of activation is employed as described herein for PAO's such as PEG." Greenwald further states that, "Those of ordinary skill in the art will realize that the foregoing list is merely illustrative and that all polymeric materials having the qualities described herein are contemplated." Greenwald explicitly teaches that HPMA can be used in place of PEG, and based on Greenwald's teaching, and ordinary artisan would immediately envision its use in place of PEG.

Furthermore, as stated in the prior Office action, Greenwald teaches the use of thiazolidine-2-thione groups bound through the nitrogen of the thiazolidine-2-thione

group to a carbonyl group that is a component of a linker at the end of the polymer chain (page 5, lines 6-8; examples 1, 5, 8, and 10; figures 2, 3, and 5). While Figures 2, 3, and 5 illustrate PEG as the polymeric component, Greenwald's teachings would clearly direct the ordinary artisan to the use of HPMA as well.

Applicants argue that the thiazolidine-2-thione groups are located along the HPMA copolymer chain in the instant invention (page 9 of the response). Applicants argue that in the embodiment wherein the thiazolidine-2-thione group is at the end of the polymer chain, a different polymerization process is used in the instant invention than that of Greenwald (page 9 of the response). Applicants argue that the linker of Greenwald cannot be the linker of the instant claims (page 9 of the response).

As acknowledged by applicants on page 9 of the response, instant claim 1 allows for the thiazolidine-2-thione group to be at the end of the polymer chain. In this case, the claim requires only that the thiazolidine-2-thione be bound through its nitrogen atom to a carbonyl group that is a component of a generic linker. It is noted that the term "linker" has not been defined in the instant specification. In fact the term "linker" does not appear in the original specification or claim set at all, but is only present in the amended claim set dated Aug. 12, 2008, submitted following the restriction requirement. Thus, the term has been given its plain meaning and has been interpreted broadly. The American Heritage Dictionary of the English Language shows "linker" as synonymous with "link", which is defined as, *inter alia*, a) A unit in a connected series of units; b) A unit in a transportation or communications system; c) A connecting element; a tie or bond. Such a "linker" could be any type of link that attaches the carbonyl group to the

rest of the polymer chain, including monomer residue or a single covalent bond. Thus, any of the examples presented in Greenwald (e.g. see Figures 2, 3, and 5) read on the claim.

Applicants argue that it is unclear which reaction the examiner was referring to when stating that "the termini of these polymers may be activated with thiazolidine-2-thione groups" (bottom of page 9 of the response).

This argument is confusing because the examiner pointed to examples 1, 5, 8, and 10; and Figures 2, 3, and 5. These examples and figures clearly teach the use of thiazolidine-2-thione to activate the polymers of the invention. It has been established *supra* that the replacement of PEG with HPMA is taught by Greenwald.

Applicants' argument that there is no functional group at the end of the HPMA polymers (page 10 of the response) is perplexing. If applicants are attempting to argue that thiazolidine-2-thione group cannot possibly be added to the end of an HPMA chain, such an argument is nonsensical in light of applicants own disclosure.

Applicants argue that Greenwald does not teach the use of HPMA homopolymers (page 10 of the response). Applicants argue that Greenwald's teaching supports a finding that the instant invention is novel.

As stated above, Greenwald teaches: "As an alternative to PAO-based polymers, effectively non-antigenic materials such as dextran, polyvinyl alcohols, carbohydrate-based polymers, hydroxypropylmethacryiamide (HPMA), and copolymers thereof, etc. and the like can be used if the same type of activation is employed as described herein for PAO's such as PEG." Since Greenwald teaches each of these types of polymers

can be used individually *and* as copolymers, the ordinary artisan would clearly recognize the teaching that each of the polymer types taught by Greenwald can be used in homopolymeric form in place of PEG (which is itself a homopolymer). The teaching that "copolymers thereof" can be used is a clearly separate embodiment. Thus, the ordinary artisan would readily envision the use of HPMA homopolymers in place of PEG as taught by Greenwald, and consistent with the definition of homopolymers used by the examiner and reiterated by applicants on page 10 of the response.

Presumably, applicants argument that Greenwald's teaching supports a finding that the instant invention is novel centers around Greenwald's teaching that HPMA polymers can be used in the invention if the same type of activation is employed as described [by Greenwald] for PEG. One of ordinary skill in the art would understand Greenwald's teaching to mean that the same type of activating group (i.e. thiazolidine-2-thione) should be used to activate the alternative polymers, should they be used in the invention. Greenwald's disclosure clearly would lead the skilled artisan to the use of HPMA polymers comprising reactive thiazolidine-2-thione groups at one end of the polymer chain. Thus, in contrast to applicants' assertion, the instantly claimed invention is not novel over the prior art. Again, it is noted that differences between the synthetic steps of the instant invention and the prior art are irrelevant since 1) such has not been claimed and 2) the instant claims are drawn to a product (i.e. polymers), not a method of making the product.

Applicants argue that HPMA is not taught because Greenwald only mentions it once (pages 9-10 of the response).

However, a reference is good for all that it teaches and all that one of ordinary skill may reasonably infer from it. In this case, Greenwald clearly teaches HPMA as an alternative to the PEG polymers that form the bulk of the exemplified polymers in the disclosure. Therefore, one of ordinary skill would immediately the use of such in Greenwald's invention and instant claims 1 and 3 are anticipated and/or obvious. It is noted that the rejection over claims 1 and 3 was made as either anticipation or obviousness, and that the examiner pointed to the Ulbrich reference to show how HPMA was used in the art at the time of the invention. The HPMA structures taught by Ulbrich, are identical to that instantly claimed.

Applicants argue that Ulbrich deals with HPMA copolymers that have a different reactive group (page 11 of the response).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case Greenwald teaches the use of thiazolidine-2-thione, and Ulbrich was relied upon to show the structure of HPMA polymers as was used in the art at the time of the invention.

Claims 1 and 3 are anticipated or obvious over Greenwald and Ulbrich.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over ULBRICH (K. Ulbrich *et al.*, J. Controlled Release (2000) 64, p. 63-79) in view of GREENWALD (R. B. Greenwald, Bioconjugate Chem. (1996) 7, p. 638-641) (hereinafter Greenwald(1996)).

3. Ulbrich discloses the synthesis and characterization of poly(HPMA) conjugates with various therapeutic molecules, including proteins, antibodies, and anti-cancer drugs such as doxorubicin (abstract). These conjugates are based on N-(2-hydroxypropyl)methacrylamide (HPMA) (page 64, left column, 2nd paragraph) and contain more than 60% of the N-(2-hydroxypropyl)methacrylamide monomer (i.e. the monomer is in a 10:1 ratio with methacryloylated *p*-nitrophenyl esters (page 66, right

column, under heading 2.6 Synthesis of polymer precursors). Ulbrich teaches activation of the relevant carboxylic acid groups using succinimidyl esters (i.e. using H-OSu) (page 66, bottom of right column; Figure 2, line), however Ulbrich do not teach the use of thiazolidine-2-thione in this capacity.

4. Greenwald(1996) teaches thiazolidine-2-thione as a reagent for protein modification that is particularly advantageous over traditional succinimidyl linkers (abstract; compounds 6 and 7). Greenwald(1996) teaches that thiazolidine-2-thione is a superior modification reagent relative to its succinimidyl counterparts because it can be used under mild conditions with only minor pH fluctuations (eliminating problems with protein denaturation encountered with succinimide reagents) and is more stable (pages 640-641, discussion section). Greenwald(1996) additionally teaches that, its advantages not withstanding, thiazolidine-2-thione is an otherwise equivalent reagent to the succinimide reagents (page 641, last paragraph of discussion section). In light of these teachings, one of ordinary skill in the art at the time the invention was made would have been motivated to substitute thiazolidine-2-thione for the succinimide type reagents taught by Ulbrich in order to obtain these advantageous properties. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to substitute thiazolidine-2-thione as a functional equivalent for succinimides and other activating reagents used by Ulbrich per the teachings of Greenwald(1996), to obtain a more stable linker in the conjugates of Ulbrich reading on instant claim 1.

5. Regarding instant claims 2 and 3, Ulbrich teaches two types of conjugation (abstract). In the first type of conjugation the pendant molecules (e.g. proteins) are

attached to the polymer via the side chain of the polymer backbone, and in the second type of conjugation the pendant molecules are attached via the end-chain functional groups of the polymers (abstract), reading on instant claims 2 and 3.

6. Regarding claim 4, while Ulbrich is silent as to the specific number of monomer units linked in the polymer chains of their invention, they teach that the conjugated polymer may have a molecular weight of 13,000 g/mol (Table 1). Taking, for example, entry 1 in Table 1, 8.2 mol% of the polymer is comprised of reactive monomer units consisting of N-methacryloylated (Ma) oligopeptides (in this case GlyPheLeuGly containing reactive groups), leaving 91.8 mol% of the polymer composed of N-(2-hydroxypropyl)methacrylamide units. 91.8 mol% of 13,000 g/mol gives an effective molecular weight for the N-(2-hydroxypropyl)methacrylamide portion of the polymer of 11,934 g/mol. Since each N-(2-hydroxypropyl)methacrylamide residue has a molecular weight of approximately 143.2 g/mol, this corresponds to about 83 N-(2-hydroxypropyl)methacrylamide monomer units (11,934 g/mol divided by 143.2 g/mol). Thus, Ulbrich teaches each element of instant claim 4 except for the use of thiazolidine-2-thione as the reactive group. However, as discussed above, in light of the teachings of Greenwald(1996), substitution of thiazolidine-2-thione for the reactive groups taught by Ulbrich is an obvious variation of this polymer conjugate. Thus, the combined teachings of Ulbrich and Greenwald(1996) read on instant claim 4.

7. Regarding claim 5, Ulbrich teaches the use of 3-mercaptopropionic acid (MPA) (i.e. 3-sulfanylpropanoic acid) as a chain transfer agent used in conjunction with succinimide reagents (page 66, right column; Figure 2, polymer precursor structure IV).

Substitution of thiazolidine-2-thione into the polymer conjugate system taught by Ulbrich would thus result in a (3-sulfanylpropanoyl)-thiazolidine-2-thione group, and is obvious by the reasoning applied above. Ulbrich teaches that the polymers of their study may have approximately 83 monomer units as discussed above. Furthermore, Ulbrich teach that the content of the oligopeptide-doxorubicin monomers can be varied in the polymerization mixture. Based on this teaching, one of ordinary skill in the art would readily have envisioned varying the oligopeptide-doxorubicin monomer content by removing it completely, resulting in a polymer of 100% N-(2-hydroxypropyl)methacrylamide units.

8. Regarding claim 6, Ulbrich teaches N-methacryloylated oligopeptides containing doxorubicin where the oligopeptides may be, *inter alia*, GlyPheLeuGly (Figure 2; Table 1), but are silent as to the specific % of N-methacryloylated oligopeptides containing doxorubicin present in their polymer system. However, Ulbrich teaches that the content of doxorubicin can be varied by changing the content of the N-methacryloylated oligopeptides containing doxorubicin (thus changing the percentage of monomer units containing doxorubicin) in the polymerization mixture (page 67, left column, bottom of the page), as would be apparent to and well within the skill of one of ordinary skill in the art. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to vary the amount of the doxorubicin-containing oligopeptide monomers in the polymerization mixture per the teachings of Ulbrich, to achieve a sufficient amount of doxorubicin in the final polymer conjugate, reading on claim 6.

9. Regarding claim 7, Ulbrich teaches the preparation of the polymer conjugates via radical precipitation copolymerization using 2,2'-azobisisobutyronitrile (AIBN), a well-known radical initiator, to begin the process of polymerization (page 64, right column; page 66, right column). Ulbrich teaches that the polymers of their study may have approximately 83 monomer units as discussed above. Furthermore, Ulbrich teaches that the content of the oligopeptide-doxorubicin monomers can be varied in the polymerization mixture. Based on this teaching, one of ordinary skill in the art would readily have envisioned varying the oligopeptide-doxorubicin monomer content by removing it completely, resulting in a polymer of 100% N-(2-hydroxypropyl)methacrylamide units. The substitution of thiazolidine-2-thione for the activating agents in the polymer conjugate system taught by Ulbrich is obvious by the reasoning applied above. Since Ulbrich teaches the use of AIBN to initiate the radical polymerization, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use AIBN as the radical initiator in conjunction with thiazolidine-2-thione per the teachings of Greenwald(1996) to initiate the polymerization reaction. The combination of these reagents would result in a (4-cyanopentanoyl)-thiazolidine-2-thione group at the chain end, reading on instant claim 7.

10. Regarding claim 8, Ulbrich teaches N-methacryloylated oligopeptides containing doxorubicin where the oligopeptides may be, *inter alia*, GlyPheLeuGly (Figure 2; Table 1), but are silent as to the specific % of N-methacryloylated oligopeptides containing doxorubicin present in their polymer system. However, Ulbrich teaches that the content of doxorubicin can be varied by changing the content of the N-methacryloylated

oligopeptides containing doxorubicin (thus changing the percentage of monomer units containing doxorubicin) in the polymerization mixture (page 67, left column, bottom of the page), as would be apparent to and well within the skill of one of ordinary skill in the art. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to vary the amount of the doxorubicin-containing oligopeptide monomers in the polymerization mixture per the teachings of Ulbrich, to achieve a sufficient amount of doxorubicin in the final polymer conjugate, reading on claim 8.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, in the absence of evidence to the contrary, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Response to Arguments

Applicants' arguments have been fully considered but are not persuasive. It is noted that, for this 103 rejection, applicants have not argued the rejections made over Ulbrich and Greenwald(1996) for claims 1-3 except to state generically that the elements missing from Greenwald and Ulbrich from the 102/103 (*supra*) rejection are

also missing from Greenwald(1996). Given that Greenwald(1996) is a completely different reference and was applied for a different reason than the former Greenwald reference (i.e. Greenwald), no proper arguments have been set forth for claims 1-3 with respect to this 103 rejection (over ULBRICH (K. Ulbrich *et al.*, J. Controlled Release (2000) 64, p. 63-79) in view of GREENWALD (R. B. Greenwald, Bioconjugate Chem. (1996) 7, p. 638-641)).

Applicants argue that the examiner relied on data in Ulbrich that have no relation to the instant invention. Applicants argue that the calculation used by the examiner is wrong because the division of molecular weight with molar ratio of monomers is incorrect.

No specific reasons for the alleged incorrectness of the calculation have been presented, and the examiner cannot agree that the calculation was improper. First, applicants incorrectly assert that the data in Ulbrich have no relation to the present invention. On the contrary, the disclosure of Ulbrich is highly relevant, and closely related to the instant invention (see the discussion in the prior Office action, also presented *supra*). The only difference between the HPMA polymers taught by Ulbrich and the instant invention is the presence of different reactive groups on the polymer. The examiner used a calculation based on data in Ulbrich to present a reasonable rationale for why the polymers taught by Ulbrich read on the limitation regarding the number of monomer units (in claims 4-8). It is noted that, while the polymers of Ulbrich differ from the instant polymers by the type of reactive groups present, the portion of the polymer used for the calculation is exactly the same. Furthermore if, *in argued*, the

calculation is in error applicants have not shown how the teachings of Ulbrich fail to meet this limitation of the claim. Applicants are invited to provide *actual evidence* based on Ulbrich that show the number of appropriate monomers of Ulbrich's polymers fall outside the ranges currently claimed (i.e. from 30-3000 monomer units for claim 4; 20-150 monomer units for claims 5 and 6; and 20-2000 monomer units for claims 7 and 8). In the absence of such evidence, applicants' arguments are unpersuasive, and the examiner's calculation is considered proper.

Applicants argue that the combination of AIBN and thazolidine-2-thione can not result in a polymer containing a (4-cyanopentanoyl)-thiazolidine-2-thione group at the chain end.

The examiner acknowledges that the use of AIBN would not result in the claimed moiety. However, the use of other radical initiators that would result in the production of the claimed (4-cyanopentanoyl)-thiazolidine-2-thione group would have been obvious to the ordinary artisan at the time of the invention. Both AIBN and 2,2'-azobis(4-cyanopentanoic acid) were known functional equivalents as radical initiators. This is evidenced by Schacht (U.S. 6,312,727), which discloses HPMA polymer based carrier vehicles for drug delivery. Schacht describes the preparation of HPMA polymers with various reactive terminal groups based on free radical addition polymerization (col. 24, Example 9) using either AIBN (Example 9, 9.1.1) or azobis(4-cyanovaleric acid) as a radical initiator (Example 9, 9.1.2). Thus, one skilled in the art would know that either AIBN or azobis(4-cyanovaleric acid), which would result in a (4-cyanopentanoyl) moiety,

would be a suitable means for preparing the polymers of Ulbrich.

The MPEP states, in relevant part: "In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958) (The mere fact that components are claimed as members of a Markush group cannot be relied upon to establish the equivalency of these components. However, an applicant's expressed recognition of an art-recognized or obvious equivalent may be used to refute an argument that such equivalency does not exist.); ** *Smith v. Hayashi*, 209 USPQ 754 (Bd. of Pat. Inter. 1980) (The mere fact that phthalocyanine and selenium function as equivalent photoconductors in the claimed environment was not sufficient to establish that one would have been obvious over the other. However, there was evidence that both phthalocyanine and selenium were known photoconductors in the art of electrophotography. "This, in our view, presents strong evidence of obviousness in substituting one for the other in an electrophotographic environment as a photoconductor." 209 USPQ at 759.). An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)." See MPEP § 2144.06.

As discussed in the prior Office action, Greenwald(1996) teaches thiazolidine-2-thione as a reagent for protein modification that is particularly advantageous over traditional succinimidyl linkers (abstract; compounds 6 and 7). Greenwald(1996)

teaches that thiazolidine-2-thione is a superior modification reagent relative to its succinimidyl counterparts because it can be used under mild conditions with only minor pH fluctuations and is more stable (pages 640-641, discussion section). Greenwald(1996) additionally teaches that, its advantages not withstanding, thiazolidine-2-thione is an otherwise equivalent reagent to the succinimide reagents (page 641, last paragraph of discussion section). In light of these teachings, one of ordinary skill in the art at the time the invention was made would have been motivated to substitute thiazolidine-2-thione for the succinimide type reagents taught by Ulbrich in order to obtain these advantageous properties. Thus, Greenwald(1996) provides a strong motivation for one of skill in the art to use the thiazolidine-2-thione group over the succinimides and other activating reagents used by Ulbrich to obtain a more stable linker in the conjugates of Ulbrich.

The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Semaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). >See also Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick, 464 F.3d 1356, 1368, 80 USPQ2d 1641, 1651 (Fed. Cir. 2006) ("Indeed, we have repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the improvement' is technology-independent and the combination of references results in a product or process that is more desirable, for example because it

is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal—and even common-sensical—we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves."). See MPEP § 2144.

In this case, Greenwald(1996) provides all the rationale one would need to modify the teachings of Ulbrich to arrive at the instantly claimed invention. The advantages taught by Greenwald(1996) are strong and explicit. Thus, one of skill in the art would be motivated to prepare the HPMA polymers having thiazolidine-2-thione as a reactive group by *any means known in the art*. Since the methods claimed in 5-7 were known in the art at the time of the invention as evidenced by Schacht, it would have been *prima facie* obvious for one to employ these methods.

Applicants are reminded that a reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976).

Applicants argue that the polymers of Ulbrich were synthesized under different conditions than the instant polymers.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., solvents and other synthesis conditions) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the

specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claims 1-8 are obvious over Ulbrich and Greenwald(1996).

Summary/Conclusion

Claims 1-8 are rejected; claims 9-16 are cancelled.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin S. Orwig whose telephone number is (571)270-5869. The examiner can normally be reached Monday-Friday 7:00 am-4:00 pm (with alternate Fridays off). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached Monday-Friday 8:00 am-5:00 pm at 0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KSO

/David J Blanchard/
Primary Examiner, Art Unit 1643